218. X-ray crystallography determines the 3D structures of proteins by: (i) crystallizing a sample of the protein; (ii) exposing the crystals to high-intensity x-rays, to give a diffraction pattern of the x-ray interaction with the crystal; (iii) viewing the intensities of the x-ray diffractions spots on the patterns; and (iv) calculating electron densities from the spots. **A5683:16-5684:13**. The electron densities indicate where atoms, such as those of amino acids, are in the crystal. Then the structures of know amino acids are matched up with the electron density patterns. Coordinates for each atom are typically entered into a PDB (protein data bank) file which eventually may be made available to the public. **A5684:20-5685:12**.

219. Machius '95 reported that the crystal structure for an inactive, calcium-depleted, cleaved form of BLA had been solved. However, this three-dimensional structure is not actually shown in the reference, nor are the atomic coordinates of the structure given. **A5725:5-8**. These coordinates are necessary to describe the 3D structure, however (**A5726:12-23**; **A5685:5-10**).

220. Machius '95 (published in March 1995) states that the coordinates for his BLA crystal structure had been deposited with the PDB and would be made available to the public in about two years. **TE-173, A8388; A5708:14-19**. In fact, the coordinates were not deposited until June 1995. **TE-118, A8251 A5716:19-5717:4**. Dr. Machius testified that he never gave the coordinates to anyone prior to March 29, 1995. **A5718:11-15**. The rotating 3D structure that Dr. Machius displayed at trial was possible because he used the coordinates; but this information was not available from the Machius '95 reference. **A5727:1-2**.

221. In the absence of atomic coordinates, Machius '95 discloses a two-dimensional cartoon of the calcium-depleted BLA structure, showing secondary structures assembled to form a representation of the crystallized protein. **TE-173, A8379 at Figure 1**; **A5726:15-23.** Like Bisgard-Frantzen, Machius '95 provides, in Figure 7, an alignment of the amino acid sequences of BLA, BSG, and BAN. Deduced secondary structures for BLA are labeled in the alignment. **TE-173, A8387; A5633:15-18; A5691:1-13**. No other crystal structures are provided or compared, however. In particular, there is no structure for *B. stearothermophilus*. **A5635:15-24**.

222. Machius '95 Figure 7 was taken from an earlier 1985 publication by Yuuki, *et al.* **TE-173, A8387; A6633:12-23**. Yuuki is also cited in Suzuki (**TE-115, A8238**). Machius added some information about the secondary structure of BLA. **A5691:12-13**. However, Dr. Machius testified at trial that a secondary structure teaches "very little more" about 3D structure than does the primary structure *i.e.*, the amino acid sequence itself. **A5688:7-12**. Neither the primary structure nor the secondary structure gives knowledge of the tertiary or 3D structure. **A5686:14-25**; **A5690:4-14**. At most, Figure 7 suggests that the 3D structures of the three alpha-amylases are likely to be similar. **A5634:23-5635:14**. This was already known from Suzuki and Bisgard-Frantzen. Protein engineers expect that the 3D structures of homologous proteins will be similar, particularly in regions where they align. **A5696:15-20; A5723:17-21**.

223. Machius '95 suggests that the amino acids of BLA corresponding to Suzuki's "region I" are found in the crystal structure as part of a "surface loop" of amino acids. **TE-173, A8384; A5703:6-18; A5709:24-5710:11; A6522:19-6523:1**. This loop is said to be enlarged by the amino acids at positions 176 and 177 of BAN, which are not present in BLA and which Suzuki deleted to make a more thermostable BAN variant. ***Id.***[4]

224. Machius '95 proposes, as one theory among many, that the enlarged loop in BAN may have increased mobility in BAN, which might explain why BAN is less thermostable than BLA. **TE-173, A8384; A5703:12-18; A5709:24-5710:11; A6522:19-6523:1**.

225. Machius '95 provides no additional information about the degree of improvement which may or may not be obtained by modifying BAN, or any alpha-amylase, in Suzuki's "Region I," whether or not that region falls within a "loop" of the crystal structure. **A5721:21-5722:5**. In particular, Machius '95 provides no information about the degree of improvement

[4] Machius '95 uses the alternative abbreviation "BAA" to denote the alpha-amylase of *Bacillus amyloliquifaciens*, aka "BAN". *See* **A5577:21-24**.

which may or may not be obtained by modifying BSG in the region I "loop." **A6529:17-19; A6550:16.**

226. The crystal structure that Machius '95 reports (but does not actually disclose) is a flawed BLA structure, because the molecule was calcium depleted and proteolytically digested. **A5729:23-5730:1; A5702:10-16; A5730:15-21.** Metal ions, such as calcium, are crucial for the function of BLA. **A5730:5-10.** However, calcium caused the Machius '95 crystals to disintegrate. **A5731:16-21.** The Machius '95 structure without calcium was deduced from a catalytically inactive protein, because the necessary calcium was removed. **A5729:23-5730:8; A6097:19-23.** The proteolytic cleavage was adjacent to the putative "loop." **A5730:24-5731:7.** This means that, there may be anomalous loose ends in the structure; the true structure is less certain, and the potential impact on function is unknown. **A5702:13-23; A5730:15-5731:11.** Dr. Machius did not determine the movement in the structural configuration caused by this cleavage. **A5731:12-15.**

227. Additionally, one of ordinary skill in the art could not locate the loop in the Machius '95 cartoon of Figure 1, and could not really determine whether the amino acids deleted by Suzuki are to be found there. The deleted 179 and 180 amino acids of the '031 patent cannot confidently be placed there either. **A6106:13-16; A5701:23-5702:1.** The entire region, from 181 to 193 in BLA was murky, and the C-terminus could not be located either. ***Id.;*** **A6099:18-25.** Genencor's expert, Dr. Zeikus could not find the alleged loop in Machius '95 without resort to information in a later Machius '98 article. **A6100:1-6101:11.** Dr. Zeikus also agrees that Machius '95 can not actually explain why BLA is more stable than BAA, in part because no 3D structure is actually disclosed, including the structure of any variant. **A6102:1-25.**

228. It was not until 1998, that Dr. Machius was able to determine the 3D structure of BLA in the presence of metal ions in an uncleaved form. **TE 175, A8591-8402; A5704:10-13.** His '95 and '98 structures differ in a number of respects. **A5729:3-7.** Machius '98 states that the structures of the calcium depleted (Machius '95) and calcium containing (Machius '98) molecules

"exhibit drastically different formations depending on whether the metal [*e.g.* calcium] ions are bound or not." **TE-175, A8397; A5727:16-5728:14.**

229. The art was confused in 1995. **A6523:10-17.** Machius '95 discusses several prior theories of BLA's thermostabilty, including those of Tomazic, Janicke, and Suzuki (concerning electrostatic interactions and hydrophobility). Machius '95 proposed its own, loop-dependent theory of thermostabilty. **TE-173, A8384; A6522:19-6523:1.** However, "none of the above-mentioned theories is able to explain the satisfactorily the enhanced thermostability of BLA." **TE-173, A8384; A6522:7-12.** Special interactions in Suzuki's regions I and II that could explain or "lead to a markedly increased thermostability" were not detected by Machius. ***Id.***; **A6518:22-6519:1; A6520:2-4.** In fact, no theory for the "why" of Suzuki's observations could be adopted or ruled out "because of the lack of the three-dimensional structures of BAA [aka BAN] and of the [Suzuki] mutants." **TE-173, A8384.** Machius '95 concluded that "further structural information on BAA is needed." ***Id.*, A8385.** *See also,* **A6103:17-22; A6105:6-9; A6517:15-6521:2; A6521:16-6522:12.**

230. Many possible factors affecting or explaining differences in thermostability were suggested in 1995. Dr. Zeikus, one of ordinary skill in the art in 1995, wrote a paper (**TE 178, A8509**) summarizing the art in 1995 and lists numerous possible stabilizing factors. These include conformational strain release, additional salt bridges, increased internal hydrophobicity, substitution of alpha helixes, shorter loop regions, and additional propylglycine residues. **A6504:12-6505:14; A6506:18-6507:4.** Dr. Zeikus' paper cited to Machius '95, as showing that additional salt bridges account for increased thermostability, not shorter loops. **A6524:2-6525:9.**

231. The Zeikus (**TE178**) paper discloses that, prior to Machius, shorter loops had already been associated with certain more thermostable proteins, but states that loops were also known to destabilize proteins. **TE-178, 8514; A5720:20-A5721:3.** Dr. Machius agrees. "Far from being a weak link in thermozymes, loops might contribute significantly to thermo stability." **A5721:9-13.** Loops can have any effect, *i.e.* a stabilizing or destabilizing influence. **A5720:20-**

5721:3. Klibanov *et al.* **(TE 117)** expressed yet another view, stating that salt bridges are responsible for thermostability. **A6514:10-25; A6517:4-10**.

232. Igarahashi, in 1998 wrote that the improved stability of the 179,180 deletion is due to increased calcium binding, not loop shortening. The deletion actually has a smaller effect in the particular Bacillus molecule studied by Igarahashi than in the BAN studied by Suzuki. **A6526:2-14; A6527:11-18; A6529:7-15**. This shows that the effect of such deletions is unpredictable. **A6529:16-19**.

(f) Spezyme Ethyl Satisfied a Long Felt Need

233. Genencor introduced Spezyme Ethyl in April of 2004. **A1006, ¶ X.** Genencor sold a number of both wild-type and engineered alpha-amylase products before then (**A5032:12-18**), including an alpha-amylase product called "Spezyme Fred." **A5035:3-9**. However, Genencor's existing alpha-amylase products did not have a sufficient combination of acid tolerance, thermostability, and low cost of production to be economically viable for liquefying mash in fuel ethanol production. **A5032:19-20**.

234. Genencor's customers were demanding an alpha-amylase product that was better suited for fuel ethanol production than Spezyme Fred. **A5036:3-7**. Genencor's commercial alpha-amylase enzyme technology in fuel ethanol was being hammered by technical performance and economic issues that made Genencor uncompetitive among these customers. **A5048:14-20; A5048:21-5049:4**.

235. Genencor's tried to improve its earlier Spezyme Fred product for the fuel ethanol market, but these efforts failed. **A5038:7-5039:11**. Frustrated, Genencor turned to Spezyme Ethyl, which it also called "EBS2." **A5032:4-8**. Spezyme Ethyl (a/k/a EBS2) promised to address both the technical and economic issues that made Genencor's other alpha-amylases uncompetitive. **A5049:5-8**. The company believed that going forward with EBS2 "was the only viable short term option." **A5049:18-24.**

(g) Spezyme Ethyl Was A Commercial Success

236. Since its April 2004 launch, Spezyme Ethyl has enjoyed great success. **A5048:14-5049:24**. In just two years, the total annual sales of Spezyme Ethyl have almost tripled. *See* **A1006, ¶Y**. Spezyme Ethyl has enjoyed great commercial success, at the direct expense of Novozymes. **A6028:14-22**.

(h) Genencor's Patent Application for Spezyme Ethyl

237. Genencor was so taken with Spezyme Ethyl that in 2004 it filed its own provisional patent application "relating to the Spezyme Ethyl technology." **TE-194, A8525**. The corresponding regular application has been published (**TE-202, A8532.1**) and boasts "novel variant alpha-amylase enzymes" wherein "the residues corresponding to R179 and G180 in *Bacillus stearothermophilus* are deleted." **TE-202, A8532.1 (Abstract); A8532.44 (claim 1)**. *See also* **A6538:22-6540:7; A6542:16-6543:5**.

238. Genencor's 2004 application was not filed until long after Novozymes filed its priority applications in 1995 (**TE-100, A702**); and after Genencor knew about the Novozymes application. **A5014:4-14, A5664:11-12.** However, Genencor pursued patent protection for Spezyme Ethyl despite the Suzuki Reference (**TE-202, A8532.14 [0013]**) and Machius '95 (***Id.*, [0095]**).

239. Genencor stated that "a need exists for an alpha-amylase which is more effective in commercial liquefaction processes" (***Id.* at A832.15 [0015]**). Its patent application also stated that a particular goal was "to provide an alpha-amylase having improved stability at high temperatures" (***Id.* at [0017]**), as well as "improved stability in the absence of calcium ion" (**A8532.24 at [0123]**).

240. Genencor stated that its application provided "a variant of a precursor *Bacillus stearothermophilus* alpha-amylase comprising deletions at one or more of the following positions R179 and G180 of the amino acid sequence shown in SEQ. ID NO. 3 and/or in a corresponding

position in an alpha-amylase which displays at least 90% identity with the amino acid sequence of SEQ. ID NO. 3." ***Id.*** **at [0018].**

241. According to Genencor's application (**TE-202**), its alpha-amylases, "exhibit altered performance characteristcs providing desirable and unexpected results." **A8532.22 at [0112]** Those "which exhibit improved thermostability will be especially useful in starch processing and particularly in starch liquefaction." ***Id.*** **at [0013].**

2. Enablement

242. Claims 1 and 3 of the '031 patent provide variants with the 179,180 deletion that have "at least 95% homology" to the parent or to SEQ. ID NO. 3. Claims 1 and 3 further specify that the variant must have alpha-amylase activity. **TE-100, A7040; A5252:18-25.**

243. The PTO Examiner specifically considered enablement of the '031 patent claims. She rejected claims that specified "at least 80% homology to SEQ. ID NO. 3" as not enabled. **TE-101, A7626.** However, she told Novozymes that the specification was "enabling for a •• amylase having at least 90% homology to SEQ. ID NO. 3." **A7721:10-11.** Novozymes amended its claims to specify variants with "at least 95% homology" and having alpha-amylase activity **(A7734)**, prompting the PTO Examiner to withdraw her enablement rejection and allow the claims.

244. The typical and by far most common result of making a random change to a protein sequence is that it will degrade the protein's properties. **A5136:22 to A5137:2.** Changing just a single amino acid can have a deleterious effect. **A5137:6-7.** Hence, the specified 179, 180 deletion, plus the required percent homology, plus the required alpha-amylase activity excludes the vast majority of theoretical variants. **A5252:18-25.**

245. Variants can readily be screened for alpha-amylase activity. For example, the '031 patent also provides an assay for the determination of alpha-amylase activity. **TE-100, A7022 at 30:55-31:27.** This assay uses commercial "Phadebas® tablets that contain a cross-

linked, insoluble blue colored starch polymer" to measure alpha-amylase activity. ***Id.*** **at 30:55-60.**

246. Dr. Borchert and his technician, Vibeke Holbo, also used a Phadebas assay to perform the experiments described in the Borchert Declaration. **TE-508, A8858 at ¶ 5** (Experimental Protocol); **A6078:24-25.**

247. Dr. Klibanov described a routine assay that he and others use to measure alpha-amylase acitivy. **A5786:14-5787:4.** Like the assays in the '031 patent and in the Borchert Declaration, Dr. Klibanov's assay uses a complex of starch with blue dye to monitor alpha-amylase activity. **A5786:21-23.**

248. Dr. Klibanov also testified that he could prepare an alpha-amylase with the two deletions 179,180 in a *B. stearothermophilus* alpha-amylase by simply following the teachings in the Suzuki paper. **A6005:18-6006:5.**

E. Enforceability

1. Inequitable Conduct

(a) The Machius '95 Reference

249. Mr. Garbell has been employed by Novozymes as registered U.S. patent attorney since November 2000. **A5004:14-20; A5006:6-17.** He has been responsible for several hundred patent applications, more than one hundred of which have issued to Novozymes in the enzyme and alpha-amylase areas. **A5006:14-17.** Mr. Garbell was responsible for prosecuting the '031 patent on behalf of Novozymes. **A5006:22-5007:11-17.**

250. Mr. Garbell was aware of his duty under 37 CFR 1.56 to present material information to the PTO during prosecution of the '031 patent. **A5654:16-22; A5676:22-5677:4.**

251. In reviewing prior art, Mr. Garbell understood some of the technical information and its import, and he consulted with an expert such as Dr. Borchert and another inventor for parts he did not understand. **A5657:1-6; 5671:16-19.** Mr. Garbell routinely consults with

inventors or other experts regarding the meaning and import of references he learns about, and he did so in the '031 prosecution. ***Id.***; **A5673:11-21.**

252. Mr. Garbell was aware of Machius '95 during the '031 patent prosecution. **A5012:8-12; A5657:11-14.** He reviewed Machius '95 with Dr. Borchert in connection with a different co-pending patent application that was involved in a PTO interference. **A5599:11-24.** The claims in that application and in the interference were specifically concerned with alpha-amylase crystal structures. **A5657:15-19; TE524.**

253. Mr. Garbell did not consider Machius '95 to have information that the PTO examiner in the '031 patent would have wanted to know for a possible rejection of the '031 patent claims. **A5672:23-5673:3.** He knew that Machius '95 contained information that was not in Suzuki, but he did not independently know or conclude (nor was he told) that any of this other information was material to the '031 patent or that it added anything important to that upon which the examiner had already relied, *i.e.*, in Suzuki and Bisgard-Frantzen. **A5672:14-17; A5673:5-10; A5673:19-21; A5675:9-20.** Mr. Garbell was aware of and consistently strove to meet his duty of disclosure to the PTO. He did not experience any doubt about the immateriality of Machius '95 or whether it should be cited to the PTO in the '031 prosecution. **A5676:25-5677:4.** Mr. Garbell did not see Machius '95 as material to the prosecution of the '031 patent. **A5662:8-12.**

254. Dr. Borchert read Machius '95 shortly after it was published and during the course of the concurrent interference. **A5591:22-5592:5; A5601:10-5603:4.** He had many conversations about Machius '95 with Mr. Garbell. **A5671:16-5672:2; A5676:4-8.** With help from Mr. Garbell, he prepared a declaration in the interference (**TE-524**), which discusses Machius '95. **A5601:10-25; A5602:6-5603:3.** Dr. Borchert did not see Machius '95 as material to the prosecution of the '031 patent, either. **A5645:21-5646:4.**

255. In all of their discussions, neither Mr. Garbell nor Dr. Borchert saw Machius '95 as relevant or material to the prosecution of the '031 patent. **A5673:11-21; A5674:1-14.**

256. There is no evidence that Mr. Garbell or any of the '031 patent inventors kept Machius '95 from the PTO examiner with any deceptive intent.

(b) The Borchert Declaration

257. On July 29, 2003, the PTO issued a rejection in the '031 patent application, asserting that claims pending at that time were obvious over Suzuki in view of the Bisgard-Frantzen PCT application. **A1007-1008; TE-101 at A7619 to A7629, at A7627-7628.** Mr. Garbell told Dr. Borchert of this rejection. **5027:15-25.** Novozymes undertook the experiments reported in the Borchert Declaration, comparing BSG parent and variant with the Suzuki BAN parent and variant because Mr. Garbell and Dr. Borchert believed Suzuki to be the closest prior art. **A5660:17-19.**

258. The Borchert Declaration and amended claims were filed in the '031 patent application on September 7, 2004 (**TE-508, A8857**). The pending claims were not rejected over Suzuki in combination with Bisgard-Frantseen at that time. **A5659:3-14.** However, the Declaration was submitted and the prior art relied upon earlier by the PTO examiner was discussed, because it was thought the examiner might apply Suzuki and Bisgard-Frantzen to the amended claims submitted along with the Declaration. ***Id.***

259. Mr. Garbell specifically informed Dr. Borchert that whether the outcome of the experiments was helpful or not, the results must be presented to the PTO. **A5662:13-18; A5665:10-19; A5666:2-11; A5677:5-21.**

260. The Borchert Declaration specifically told the PTO examiner the actual temperature and calcium concentration used in the experiments. **A5666:23-5667:4; TE-508, A8858, ¶5** ("The temperature of 80 degree Celsius was chosen as the highest temperature where both BAN and BSG wild type and derived variants could be reliably compared.") **TE-508; A8859, line 3** (0.1 mM calcium chloride). **A5667:24-5668:1.** These were industrially relevant conditions. **A6092:15-25; A6095:12-6098:17; A6535:24-6536:25; A5025:8-15.**

261. In working on the Declaration, Mr. Garbell had before him only the data that appears in the Declaration. He did not have and was not aware that any additional or raw data had been excluded. **A5664:25-5665:9.**

262. Dr. Borchert did not know that measurements had been excluded by Ms. Holbo for a BSG variant sample at 2881 minutes when he executed the declaration and when he had the interview with the Examiner. He did not know that these measurements had been excluded until this litigation. **A5643:13-17; A6092:15-25; A6095:12-6096:17; A6535:24-6536-25; A5025:8-15.**

263. One BSG variant sample at 2881 minutes had evaporated, and both of its readings could not be used. **A6079:5-14; A5643:17-24; A6549:4-20.**

264. Two BSG wild-type readings at 20 and 40 minutes were contaminated by substrate in the samples and could not be used, but the two parallel readings were acceptable and were used. **A6080:3-14; A5811:5-5812:4.**

265. Dr. Borchert did know that both data point readings for a sample of BSG delete at 2940 minutes were excluded from the results in the Declaration. **A5645:2-17.** These points were properly excluded because they were unreliable. One reading showed more than 100% activity after two days; the other reading was so widely different that it could not be used with confidence. Of the two data points, one measured above 130 percent and the other as low as 56 percent; a difference of 120-130 percent between two activity measurements which should have been identical for a single sample. The sample itself was suspect and neither measurement could be used with any confidence. **A5645:2-17; A6546:1 - A6547:19.**

2. <u>Prosecution Laches</u>

266. Novozymes diligently prosecuted the family of applications from which the '031 patent issued, and other patents have issued from this family. **TE-101, A7002, A7042, A7136.** Application No. 10/025,648 (which issued as the '031 Patent) was a division of Application No. 09/354,191). ***Id.*** The '191 Application issued as U.S. Patent No. 6,297,038. ***Id.*** The '191

Application was a continuation of Application No. 08/600,656. ***Id.*** The '656 Application issued as U.S. Patent No. 6,093,562. ***Id.***

267. These applications share the same specification, and claim different embodiments of the disclosed alpha-amylase variants. Novozymes prosecuted different sets of claims in each case, and in due course obtained several patents, including the '031 patent now in suit. Furthermore, the '031 prosecution file (**TE-101**) reveals a standard prosecution history. Office Actions were issued in the usual way, and were duly acted on, within the time periods set by statute.

268. Novozymes' exchange with the PTO can be tracked, in brief, as follows. **TE-101, A7042-7132, A7133-7235** (Preliminary Amendment, December 19, 2001); **A7236** (Notice of Missing Parts, February 20, 2002); **A7237-7240** (Novozymes' Response, April 19, 2002); **A7241-7618** (Information Disclosure Statement, June 12, 2002); **A7619-7631** (First PTO Action, July 29, 2003); **A7632-7716** (Novozymes' Response, January 14, 2004); **A7717-7731** (Second PTO Action, April 6, 2004); **A7733, A7798-7799** (PTO Interview, September 3, 2004); **A7732-7760** (Novozymes' Response, September 7, 2004); **A7791-7802** (PTO Notice of Allowance, September 21, 2004).

269. By December 2001, Novozymes was already pursuing the claims for the subject matter at issue this case (**TE-101, A7045-7048**), well before Genencor introduced Spezyme Ethyl in April 2004. **A-1006**; **A5663:13-22**. Those early claims included "[a] variant of a parent alpha-amylase enzyme" having the 179,180 deletion, and "at least 80% homology to SEQ. ID NO. 3." **TE-101, A7045-7048** The PTO initially rejected these claims as obvious. Novozymes then did some work to overcome that rejection, including the experiments in the Borchert Declaration. **A1007-1008; TE-101, A7619-7631, A7717-7760; A7791-7802.**

270. The application that became the '031 patent was published on April 3, 2004, and Genencor had notice that Novozymes was pursuing these claims before Spezyme Ethyl was launched in April 2004. **A5663:16-5664:21.**

II. CONCLUSIONS OF LAW

A. Claim Construction

271. Claim construction is a threshold inquiry in any assessment of patent infringement. *Athletic Alternatives v. Prince Mfg.*, 73 F.3d 1573, 1578 (Fed. Cir. 1996). The determination of patent infringement is a two step process. First, the meaning of the patent claim is ascertained, and second, the structure or process under consideration is compared with the claim as properly interpreted. *North Am. Container, Inc. v. Plastipak Packaging, Inc.*, 415 F.3d 1335, 1344 (Fed. Cir. 2005); *see also Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976, 979 (Fed. Cir. 1995) *(en banc), aff'd*, 517 U.S. 370 (1996).

272. The first step in any invalidity analysis is claim construction. The meaning of the patent claim is ascertained. *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333 (Fed. Cir. 2002); *Rockwell Int'l Corp. v. United States,* 147 F.3d 1358, 1362 (Fed. Cir. 1998); *see also Markman*, 52 F.3d at 976, 979.

273. The same claim interpretation must be used for infringement and validity. *Kegel Co. v. AMF Bowling, Inc.*, 127 F.3d 1420, 1429 (Fed. Cir. 1997) (*quoting SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 882 (Fed. Cir. 1988)); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 842 F.2d 1275, 1279 (Fed. Cir. 1988).

274. Claim construction is a question of law, exclusively within the province of the court. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1455 (Fed. Cir. 1998) (*en banc*); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

275. A proper claim construction must give meaning to every claim limitation. *Harris Corp. v. IXYS Corp.*, 114 F.3d 1149, 1152 (Fed. Cir. 1997).

276. When construing a patent claim, one should look first to the intrinsic evidence of record, *i.e.*, the patent itself, including the claims, the specification, the prosecution history before the U.S. Patent and Trademark Office ("PTO"), and the cited prior art. *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1152 (Fed. Cir. 1997). This evidence "is the most significant source of

the legally operative meaning of disputed claim language." *Vitronics*, 90 F.3d at 1582. If this public record clearly establishes the meaning of the claim, the inquiry is complete. *Id.* at 1583.

277. Claim construction begins most fundamentally with the language of the claims. *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 989 (Fed. Cir. 1999); *Bell Communications Research v. Vitalink Communications Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995). "[B]edrock principle" is that "the claims of a patent define the invention." *See Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004); *Markman*, 52 F.3d at 980; *Vitronics*, 90 F.3d at 1582.

278. The patent document is paramount. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315-17 (Fed. Cir. 2005) (*en banc*). It is meant to be a "concise statement for persons in the field." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1119 (Fed. Cir. 2002); it will guide the person of ordinary skill to a proper understanding of the claims. "Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim … but in the context of the entire specification." *Phillips*, 415 F.3d at 1313.

279. The words of a claim are given their ordinary meaning to one skilled in the art, unless it appears from the patent and prosecution history that the words were used differently by the inventors. *Phillips*, 415 F.3d at 1312; *Vitronics*, 90 F.3d at 1582. Common words in a claim unless the context suggests otherwise, should be interpreted according to their ordinary meaning "[w]ithout an express intent to import a novel meaning to them." *York Prods., Inc. v. Central Tractor & Farm Family Ctr.*, 99 F.3d 1568, 1572 (Fed. Cir. 1996). Other considerations include the context of words surrounding a claim term, *ACTV v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003), as well as similarities and differences among the claims. *Phillips*, 415 F.3d at 1314-15.

280. The ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention (*i.e.*, as of the effective filing date of the patent application), "unless it is apparent from the patent and the

prosecution history that the invention used the term with a different meaning." *Hoescht Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996); *Phillips*, 415 F.3d at 1313; *see also Innova/Pure Water*, 381 F.3d at 1116.

281. "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Phillips*, 415 F.3d at 1314; *see also York Prods.*, 99 F.3d at 1572. (Common words normally accorded ordinary meaning). In such circumstances, dictionaries may be helpful. *Phillips*, 415 F.3d at 1314; *Inverness Med. v. Warner Lambert Co.*, 309 F.3d 1373, 1378 (Fed. Cir. 2002); *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1346 (Fed. Cir. 2003). However, a non-scientific dictionary may not be proper for defining a technical term. *See, e.g., AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1247-48 (Fed. Cir. 2001). This extrinsic evidence "can shed useful light on the relevant art" but is far "less significant than the intrinsic record." *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004) (*citation omitted*). Expert and inventor testimony, dictionaries and treatises may provide background guidance. *Phillips*, 415 F.3d at 1318-19. However, "[u]ndue reliance on extrinsic evidence poses the risk that it will be used to change the meaning of claims in derogation of the 'indisputable public records consisting of the claims, the specification and the prosecution history.' *Id.* at 1319 (*citation omitted*).

282. A court may receive extrinsic evidence to educate itself about the underlying technology, but cannot use extrinsic evidence to arrive at a claim construction that is inconsistent with a construction that is mandated by the intrinsic evidence. *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998).

283. The claims "must be read in view of the specification, of which they are a part." *Markman*, 52 F.3d at 979; *Phillips*, 415 F.3d at 1315. "The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication."

Vitronics, 90 F.3d at 1582. When the specification is acting as a dictionary, expressly defining a term used in the claims, it is "the single best guide to the meaning of a disputed term" *Id.*

284. "The best source for understanding a technical term is the specification from which it arose, informed, as needed, by the prosecution history." *Multiform Desiccants, Inc., v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998); *see also*, *Phillips*, 415 F.3d at 1315-16. This is the intrinsic record from which a correct claim construction proceeds. *Vitronics*, 90 F.3d at 1582. The prosecution history, though relevant, "often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Id.*

285. Although it is the best guide, the specification cannot be used to alter the claims, as by "reading a limitation from the written description into the claims," or by adding "extraneous limitations" into a claim. *Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 950 (Fed. Cir. 1993); *SciMed Life Sys, Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1377, 1340 (Fed. Cir. 2001). Extraneous limitations are those that would be added into a claim from the specification "wholly apart from any need to interpret what the patentee meant by particular words and phrases" in the claims. *Id.* (citation omitted)

286. Likewise, a claim cannot be limited to the patent examples. *Phillips*, 415 F.3d at 1323; *SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004).

287. A claim construction that does not encompass a disclosed embodiment is "rarely, if ever, correct." *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1355 (Fed. Cir. 1998) (*quoting Vitronics*, 90 F.3d at 1583).

288. "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

289. Claims 1, 3 and 5 of the patent are directed to variant alpha-amylases that have a deletion of the amino acids at positions equivalent to 179,180 of SEQ. ID NO. 3 in the patent. **A1005; TE-100, A7040**. Claim 1 compares the amino acid sequence of the variant to the amino

acid sequence of its parent, to determine, as a "percent homology," how many residues of the variant are identical in the parent. **TE-100, A7040 at 65:11-17; A5141:6-20.** Claim 3 compares the amino acid sequence of the variant to the amino acid sequence of SEQ. ID NO. 3, to determine how many residues of the variant are identical SEQ. ID NO. 3. **TE-100, A7040 at 65:21-66:12; A5145:5-5146:20.** In claim 5, the 179,180 deletion is the only difference between parent and variant. **TE-100, A7040 at 66:17-20; A5147:4-23.**

1. Claim 1 of the '031 Patent

290. Claim 1 of the '031 patent reads as follows (**TE-100, A7040**):

> A variant of a parent *Bacillus stearothermophilus* alpha-amylase, wherein the variant has an amino acid sequence which has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase and comprises a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering, and wherein the variant has alpha-amylase activity.

291. Here, the intrinsic evidence is sufficient for construing the claim terms, as claim 1 is unambiguous and clear. The '031 patent specification expressly defines certain terms recited in claim 1. The remaining terms should be given their ordinary meanings.

292. The preamble, *i.e.*, introduction portion, of claim 1 recites "[a] variant of a parent *Bacillus stearothermophilus* alpha-amylase." Ordinarily, a claim preamble that simply states a purpose or intended use of a claimed composition is not a "positive claim" limitation. However in this instance, the preamble is necessary to give "life and meaning" to the claim and, therefore, is a "positive" claim limitation. *See Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989) ("[The] preamble in this instance does not merely state a purpose or intended use for the claimed structure ... Rather, those words do give 'life and meaning' and provide further positive limitations to the invention claimed"). Here, the preamble specifies the particular type of enzyme claimed.

293. The term "variant" is used interchangeably with "mutant" (**TE-100 at A7010, 5:49-50**) and is the result of the deletion, substitution, or insertion of amino acids relative to a parent alpha-amylase. ***Id.* at A7009, 3:59-67.** *See also*, **A5138:23-5138:20.** This is the ordinary

usage of the term "variant" in protein engineering. **A5138:23-5139:9**; **A5203:2-11**; **A5171:17-5172:25**.

294. Specifically, the '031 patent teaches (TE-100 at A7009, 3:59-67) that:

> The variants of the invention are variants in which (a) at least one amino acid residue of the parent alpha-amylase has been deleted; and/or (b) at least one amino acid residue of the parent alpha-amylase has been replaced (*i.e.*, substituted) by a different amino acid residue; and/or (c) at least one amino acid residue has been inserted relative to the parent alpha-amylase.

295. In sum: A "variant" is an engineered protein that is the result of the deletion, substitution or insertion of amino acids relative to an unaltered protein.

296. The specification also teaches that a parent is an antecedent protein which is altered to provide a variant protein. **TE-100, A7008 at 1:21-24,** ("variants having improved properties relative to the parent enzyme); ***Id.* at 2:61-65** ("variants which -- relative to their parent alpha-amylase -- possess improved properties"); ***Id.* at 3:30-35** (goal is to improve the stability of certain alpha-amylases obtainable from Bacillus strains); ***Id.*, 7009 at 3:18-23** (improve parent alpha-amylase "by judicial modification of one or more amino acid residues in various regions of the amino acid sequence of the parent"). The parent proteins are "alpha-amylases which are obtainable from *Bacillus* strains," selected for their starch removal performance. ***Id.*, A7009 at 3:10-14**. Non-limiting examples are disclosed (***Id.* at 3:25-42**), and other parents are also suitable. ***Id.*, A7011 at 7:52-67**. The ordinary meaning of "parent" in protein engineering is in accord with this usage in the specification. See, e.g. **A5175:6-7; A5203:5-11**.

297. In sum: a "parent" is an unaltered protein that is modified by the deletion, substitution, or insertion of amino acids to make a variant protein.

298. Claim 1 also provides that the parent is a "*B. stearothermophilus* alpha-amylase" and the resulting variant has "alpha-amylase activity." **TE-100, A7040.** This is the ability to catalyze reactions which break down and liquefy starch. **A1003**. *B. stearothermophilus* is one species of the *Bacillus* genus of bacteria. **A1005**. The alpha-amylase originates from a *B.*

stearothermophilus organism, i.e. it is the alpha-amylase produced by a *B. stearothermophilus* alpha-amylase gene.

299. In sum: a "Bacillus stearothermophilus alpha-amylase" is the functional enzyme product that is actually produced of the alpha-amylase gene from a Bacillus stearothermophilus organism.

300. The claim 1 variants have, "an amino acid sequence which has at least 95% homology to the parent *B. stearothermophilus* alpha-amylase." **TE-100, A7040.** The meaning of "percent homology" in the context of the invention, is discussed at **TE-100, A7009, 4:36-49.**

301. The patent equates "percent homology" with "percent identity" (***Id.***; **A1005**), and teaches how to make this determination. "The GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used …." **TE-100, A7009, 4:36-49; A5525:5-9.**

302. The patent also directs the artisan to use alignment algorithms according to Lipman & Pearson (**TE-100 at 4:36-49**), however there is no dispute in this case about the proper alignment of the relevant sequences.

303. The '031 patent "clearly states that the GAP program of GCG may suitably be used. That leads to a particular calculation of percent identity." **A5146:14-5147:1.** *See also*, **TE-202, A8532.17 at [0054-56].** Two sequences are aligned according to known algorithms which find an optimum number of matches between them. **A1005, ¶¶N-O; A5107:21-5108:2; A5108:21-5109:10.**

304. GAP GCG calculates percent identity as a percent comparison of the number of identical matches between two sequences. "Percent identify takes the sum of all the matching residues where there is a corresponding part in both sequences." **A5110:22-25;A5111:2-6**

305. In sum: "Percent Homology," as defined by the '031 patent, means a percent identity calculation according to the standard whereby the number of exactly matching amino acid residues in two sequences is compared to the total number of residue positions that are

present in both sequences, expressed as a percent, *e.g.* as implemented by the GAP GCG program.

306. Each claim 1 variant, compared to its parent, "comprises a deletion of amino acids 179 and 180 using SEQ. ID NO. 3 for numbering." **TE-100, A7040.** The transition term "comprises" in a patent claim is "open-ended" and means that the claim does not exclude additional, unrecited components such as, for example in this case, other amino acid deletions, substitutions, or additions. *A.K. Steel Corp. v. Sollac*, 344 F.3d 1234, 1239 (Fed. Cir. 2004); *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1178 (Fed. Cir. 1991); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1271 (Fed. Cir. 1986).

307. SEQ. ID NO. 3 is set forth in the '031 patent. "Using SEQ. ID NO. 3 for numbering" means that SEQ. ID NO. 3 is a reference; it is not claimed as a parent. The positions of amino acids in an alignment are assigned according to equivalent positions (residue numbers) in SEQ. ID NO. 3. In claim 1, the residues of a parent sequence that align with positions 179,180 of SEQ. NO. 3 are present, but they are not present in the aligned variant. This is customary in the protein engineering field. **A5142:5-23; A5143:3-10; A5639:5-18.**

308. In sum: "A deletion of amino acids 179 and 180 using SEQ. ID NO. 3 for numbering" means that the amino acids present at positions 179 and 180 of the parent are deleted for the variant, when the amino acid positions of the aligned parent and variant are numbered according to amino acid position numbers of SEQ. ID NO. 3.

309. "Alpha-amylase activity" means: An enzyme that is able to break apart starch complexes and convert starch into smaller, simpler groups of glucose molecules by degrading or breaking specific chemical bonds called the "alpha-1,4-glucosidin bonds," between the groups of glucose molecules that make up a complex starch molecule." **A1003.**

310. In summary, Claim 1 of the '031 patent claims a "variant" with a different amino acid sequence (*i.e.*, having been deliberately modified by one or more substitutions, insertions or deletions) from a "parent" alpha-amylase (*i.e.*, a parent protein expressed by the alpha amylase

gene) of a bacteria from the species *Bacillus (Geobacillus) stearothermophilus*. When aligned with the parent alpha-amylase's amino acid sequence, the variant's amino acid sequence is at least 95% identical to the parent's amino acid sequence, using an algorithm for calculating percent identity of or equivalent to that of GAP GCG. This algorithm measures how much of the variant is identically present in the parent. In addition, the variant's amino acid sequence differs from the parent by at least the deletion of amino acids at positions aligning with amino acids 179 and 180 of SEQ. ID NO. 3. The claimed variant also has the activity of an alpha-amylase enzyme – *i.e.*, the variant has the ability to break down the alpha-1,4-glucosidic bonds in starch.

2. Claim 3 of the '031 Patent

311. Claim 3 of the '031 Patent reads as follows (TE-100, A7040):

> A variant alpha-amylase, wherein the variant has at least 95% homology to SEQ. ID NO. 3 and comprises a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering and wherein the variant has alpha-amylase activity.

312. Claim 3 differs by providing a variant alpha-amylase with at least 95% homology to SEQ. ID NO, 3 (not to a "parent"). The same 179, 180 deletion using SEQ. ID NO. 3 for numbering is called for, as is alpha-amylase activity. **A7040; A1005**. The language "variant alpha-amylase" (not "variant of a parent") means that the variant is an altered alpha-amylase, but claim 3 does not require sequence comparison to a parent. Instead, the variant is compared with SEQ. ID NO. 3. **TE-100, A7040; A1005, ¶T; A5145:21-25**. The "percent homology" comparison is also with SEQ. ID NO. 3. ***Id.***

313. In summary, claim 3 of the '031 patent should be construed as being directed to a "variant" alpha-amylase enzyme. When aligned with SEQ. ID NO. 3 for the '031 patent, the sequence of the claimed variant is at least 95% identical to SEQ. ID NO. 3, using an algorithm for calculating percent identity of or equivalent to that of GAP GCG. This algorithm measures how much of the variant is identically present in the parent. At the same time, the claimed variant's amino acid sequence differs from SEQ. ID NO. 3 at least by a deletion of amino acids aligning at positions 179 and 180 of SEQ. ID NO. 3 (and may also contain additional amino acid

substitutions, insertions and/or deletions). The claimed variant also has the activity of an alpha-amylase enzyme – *i.e.*, it can break down the alpha-1,4-glucosidic bonds in starch.

3. Claim 5 of the '031 Patent

314. Claim 5 of the '031 Patent reads as follows (TE-100, A7040):

> A variant of a Bacillus stearothermophilus alpha-amylase, wherein the alpha-amylase variant consists of a deletion of amino acids 179 and 180 using SEQ. ID NO. 3 for numbering.

315. Several of the terms in claim 5 are also found in claims 1 and 3. These terms have the same meaning in claim 5. *Southwell Techs. V. Cardinal IG Co.*, 54 F.3d 1570, 1579 (Fed. Cir. 1995).

316. The preamble of claim 5 recites "a variant of a *Bacillus stearothermophilus* alpha-amylase, wherein the alpha-amylase variant consists of a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering." **TE-100, A7040; A1006**. This means that the only difference between the unmodified *B. stearothermophilus* alpha-amylase and the variant is the 179,180 deletion. **A5147:12-23**.

317. In summary, claim 5 of the '031 patent should be construed as being directed to a "variant" alpha-amylase enzyme. When aligned with the parent alpha-amylase's amino acid sequence, the variant's amino acid sequence differs from the parent by *only* the deletion of amino acids at positions aligning with amino acids 179 and 180 of SEQ. ID NO. 3. The claimed variant also has the activity of an alpha-amylase enzyme – *i.e.*, the variant has the ability to break down the alpha-1,4-glucosidic bonds in starch.

B. Genencor's Alpha-amylase Product Infringes '031 Claims 1, 3 and 5

318. Once the claims have been properly construed, the accused alpha amylase must compared with the claim as properly interpreted. *North American Container*, 415 F.3d at 1344; *see also Markman.*, 52 F.3d at 976, 979.

319. A United States patent is infringed directly when someone without authority makes, uses, offers to sell, or sells within the United States or imports into the United States the patented invention during the term of the patent. 35 U.S.C. §271(a).

320. The protection granted by a United States patent is defined by the claims of the patent as read literally or under the doctrine of equivalents. Establishing literal infringement requires that every limitation set forth in a claim must be found in an accused product or process exactly. *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331-32 (Fed. Cir. 2004).

321. The question of infringement is a factual one, and the patentee must prove infringement by a preponderance of the evidence. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1339, 1355 (Fed. Cir. 2005). This "simply requires proving that infringement was more likely than not to have occurred." *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir., 2005).

322. Every limitation of '031 patent claims 1, 3, and 5, is found exactly in Genencor's Spezyme Ethyl alpha-amylase product. Therefore, literal infringement is present. *Norian Corp.*, 363 F.3d at 1331-32. (literal infringement exists where the accused product embodies every limitation of a patent claim.)

1. Spezyme Ethyl Infringes Claim 1 of the '031 Patent

323. Claim 1 of the '031 claims a variant of a parent *B. stearothermophilus* alpha-amylase. **TE-100, A7040**. Spezyme Ethyl is derived from G997, a *B. stearothermophilus* alpha-amylase. G997 is the parent of Spezyme Ethyl. **TE-194, A8525; TE-161, A8365-66; A5039:12-5040:8; A5045:16-19; A5046:10-13; A5148:8-5149:18.**

324. Spezyme Ethyl is a "variant": it is an engineered protein that is the result of the deletion, substitution, or insertion of amino acids relative to an unaltered protein: G997. ***Id.***

325. The G997 "parent" is an unaltered protein that is modified by the deletion, substitution, or insertion of amino acids to make a variant protein: Spezyme Ethyl. ***Id.*** G997 is also a "B. stearothermophilus alpha-amylase": it is the enzyme protein that is actually produced

by the alpha-amylase gene from a wild-type B. stearothermophilus organism: the gene from "Bacillus stearothermophilus strain ASP154, ATCC deposit no. 39,709" a/k/a G997. **TE-194, A8521, A8525; TE-161, A8365-66; A5259:8-22.**

326. Spezyme Ethyl is unequivocally "a variant of a parent B. stearothermophilus" according to claim 1.

327. Claim 1 specifies that the variant has alpha-amylase activity. **TE-100, A7040.** The meaning of an "alpha-amylase" and its activity is undisputed. **A1003.** Genencor admits that Spezyme Ethyl has alpha-amylase activity. **TE-194, A8525; TE-134, A8355; A5159:17-23.**

328. Claim 1 specifies that the variant differs from the parent by a deletion of the residues at positions 179 and 180 of the parent, "using SEQ. ID NO. 3 for numbering." **TE-100, A7040.** Additionally, "the variant has an amino acid sequence which has at least 95% homology to the parent." **TE-100, A7040.** When Spezyme Ethyl and G997 are aligned, and percent homology is calculated according to the '031 paten specification and claims, Spezyme Ethyl has the claimed 179,180 deletion and has at least 95% homology to G997. *See, e.g.*, **TE-126, A8347-8348; A5116:18-5117:1; A5071:25-5072:10; TE-194, A8521-22; A5113:22-5115:20; A5158:18-5159:1; A5118:22-A5119:16; A5160:7-15; A5161:7-12.**

329. Per claim 1, Spezyme Ethyl "comprises a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering": the amino acids present at positions 179,180 of the parent are deleted from the variant, when the amino acid positions of the aligned parent and variant are numbered according to amino acid position numbers of SEQ. ID NO. 3. **A5119:22-5120:7; A5159:2-14; A5162:9-22.**

330. All of the limitations of claim 1 are found in Spezyme Ethyl. It is a variant of a parent *B. stearothermophilus* alpha-amylase having the amino acid sequence of G997. When the Spezyme Ethyl sequence is aligned to the G997 sequence, they are identical, except for the two amino acids at positions 179 and 180. These positions are the same as positions 179 and 180 of SEQ. ID NO. 3 in the patent. These two amino acids are present in G997 and are deleted in

Spezyme Ethyl. When percent identity is calculated, using the "exact match" algorithm of GAP GCG, Spezyme Ethyl has 100% homology to G997, which is "at least 95%." **TE-126, A8347-48; A 5113:22-5144:20; A 5116:18-5118:15; A 5158:16-5159:1.**

2. Spezyme Ethyl Infringes Claim 3 of the '031 Patent

331. Claim 3 specifies a variant alpha-amylase. **TE-100, A7040.** Spezyme Ethyl is derived from and is a variant of G997, a *B. stearothermophilus* alpha-amylase. **TE-194, A8525; TE-161, A8365-66; A5039:12-5040:8; A5045:16-19; A5046:10-13; A5148:8-A5149:8.**

332. Claim 3 specifies that the variant differs from SEQ. ID NO. 3 by a deletion of the two amino acids at positions 179 and 180, "using SEQ. ID NO. 3 for numbering." **TE-100, A7040.** Spezyme Ethyl has this deletion compared to SEQ. ID NO. 3. **TE-127, A8349-50; TE-100, A7009 at 4:36-45.** *See also,* **A5116:18-5117:1.** The amino acids aligned at positions 179 and 180 of SEQ. ID NO, 3 are deleted in Spezyme Ethyl. **TE-127.**

333. A percent identity of 98.967% was calculated for the alignment of Spezyme Ethyl and SEQ. ID NO. 3. **TE-127, A8349; A5118:22-5119:16; A5160:7-15; A5161:7-12.** This is "at least 95%." **TE-100, A7040.**

334. Claim 3 is infringed. Spezyme Ethyl is a "variant alpha-amylase," and more specifically is derived from an identified *B. stearothermophilus* alpha-amylase strain. **TE-194, A8521, 8525.** When the Spezyme Ethyl sequence is aligned to SEQ. ID NO. 3, the two amino acids at positions 179 and 180 are deleted. **TE-127.** When percent identity is calculated, Spezyme Ethyl shows a 98.967% homology to SEQ. ID NO. 3, which is "at least 95%." ***Id.***

3. Spezyme Ethyl Infringes Claim 5 of the '031 Patent

Claim 5 provides a "variant of a *Bacillus stearothermophilus* alpha-amylase." **TE-100, A7040.** As above, Spezyme Ethyl is derived from and is a variant of G997, which in turn is an alpha-amylase that originates from a specific *B. stearothermophilus* alpha-amylase. **TE-194, A8521, 8525**; §§II(B)(1,2) *supra* (claims 1 and 3). Claim 5 also states that the variant "consists of a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering." **TE-100, A7040.** As

shown, the Spezyme Ethyl sequence differs from the G997 sequence by just these two amino acids. The residues RG at positions 179,180 of G997 are deleted in Spezyme Ethyl, using the same position numbering as SEQ. ID NO. 3. **TE-126; A5147:12-23; A5259:23-5260:3, A5260:21-5261:5.** All of the limitations of claim 5 are met by Spezyme Ethyl.

335. In sum, Spezyme ethyl falls within each claims 1, 3, and 5. *See also,* **A5137:24-5138:5; A5162:23-5163:2.**

C. The '031 Patent Is Valid

336. An issued patent is presumed valid. 35 U.S.C. § 282; *see also Robotic Vision Sys., Inc. v. View Eng'g, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir. 1999) ("There is a strong presumption of validity for issued patents."); *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) ("Issued patents have a strong presumption of validity in infringement proceedings."). Accordingly, the heavy burden of showing invalidity rests with defendants, who must prove invalidity by clear and convincing evidence. *Robotic Vision*, 189 F.3d 1370 at 1377; *Al-Site*, 174 F.3d at 1323.

337. The burden of establishing the invalidity of patent claims in light of prior art may be especially difficult when that same prior art was considered by the Patent Examiner during prosecution of the patent application. *Metabolite Labs., Inc. v. Laboratory Corp. of Am. Holdings*, 370 F.3d 1354, 1368 (Fed. Cir. 2004) (*citing Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990)), *cert. granted*, 126 S. Ct. 601 (2005); *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1353 (Fed. Cir. 2001) (*quoting American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359-60 (Fed. Cir. 1984).

338. Clear and convincing evidence is evidence that produces an abiding conviction that the truth of a factual contention is highly probable. *Colorado v. New Mexico,* 467 U.S. 310, 316 (1984). Proof by clear and convincing evidence is thus a higher burden than proof by a preponderance of the evidence. *United States v. Mack*, 229 F.3d 226, 230 (3d Cir. 2000); *Price v.*

Symsek, 988 F.3d 1187, 1193 (Fed. Cir. 1993); *Johns Hopkins Univ. v. CellPro, Inc.*, 978 F. Supp. 184, 190 (D. Del. 1997).

1. The '031 Patent is Not Obvious

339. An invention that is patentable in the United States must be, *inter alia*, non-obvious under 35 U.S.C. §103(a). An invention is not patentable if, although the invention is not identically disclosed or described in the prior art, the differences between the invention and the prior art are such that the invention as a whole would have been obvious at the time of the invention to a person having ordinary skill in the relevant art. 35 U.S.C. §103(a); *Graham v. John Deere Co.*, 383 U.S. 1, 13-14 (1966).

340. "The obviousness standard, while easy to expound, is sometimes difficult to apply. It requires the decision maker to return to the time the invention was made." *Uniroyal, Inc. v. Rudkin-Wildy Corp.*, 837 F.2d 1044, 1050 (Fed. Cir. 1988). It is improper, therefore to use hindsight when deciding an invention is obvious. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991)

341. Whether an invention would have been obvious is a legal conclusion based on underlying findings of fact. *In re Dembiczak*, 175 F.3d 994, 998 (Fed. Cir. 1999). The determination is based upon (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the art, and (4) objective evidence of secondary considerations. *Graham*, 383 U.S. at 17-18.

342. Most inventions arise from a combination of old elements, and each element may often be found in the prior art. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). The mere identification of each element in the prior art, however, is insufficient to defeat the patentability of the combined subject matter as a whole. *Id.* Rather, one must show a motivation to combine the references; *i.e.*, "reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to

modify the teachings of that reference. *See ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984); *Genzyme Corp. v. Atrium Med. Corp.*, 315 F. Supp. 2d 552, 564 (D. Del. 2004).

343. A patent claim is obvious over a combination of prior art references only when "the prior art would have suggested to one of ordinary skill in the art that [the claimed invention] should be carried out and would have a reasonable likelihood of success. . . . Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical,* 837 F.2d 469, 473 (Fed. Cir. 1988); *see also* 35 U.S.C. §103.

344. An invitation to experiment alone cannot make an invention obvious. *In re Dow*, 837 F.2d at 473. In particular, success is not reasonably expected when its kind or degree was unpredictable. *In re Soni*, 54 F.3d 746, 750-51 (Fed. Cir. 1995) (substantially improved and unexpected). An invention is not obvious when its results were unexpected. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Likewise, an invention that satisfies a long-felt need, overcomes advanced past failures, or is a distinct commercial success, is not likely to be obvious. *Fromson v. Advanced Offset Plate,* 755 F.2d 1549, 1556-58 (Fed. Cir. 1985) ("evidence of secondary conditions ... 'may also be the most probative and cogent evidence in the record'" citation omitted)).

345. One may rebut a *prima facie* case of obviousness by providing surprising or unexpected results. "An applicant may make this showing with evidence" that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would find surprising or unexpected ... The basic principle behind this rule is straightforward - that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product may yield substantially different results." *In re Soni*, 54 F.3d at 750; *see Ortho Pharm., Corp. v. Smith*, 959 F.2d 936,

943 (Fed. Cir. 1992) ("... one could not predict the effect of small structural changes on the biological activity.")

346. During the '031 prosecution, the PTO Examiner considered the *B. stearothermophilus* 179,180 deletion for obviousness under 35 U.S.C. §103(a). She rejected claims to these variants based on a combination of Suzuki (**TE-115**) and Bisgard-Frantzen (**TE-177**). **A1007, ¶AA; A5010:23-5011:16; TE-101 at A7627-7628.**

347. Suzuki describes mutants of an alpha-amylase enzyme from another *Bacillus* species – *B. amyloliquefaciens* ("BAN" or "BAA"). Some of these mutants were modified to be more like a different alpha-amylase, from *B. licheniformis* ("BLA"), and they had improved thermostability compared to the wild-type BAN alpha-amylase they came from. One BAN mutant had a deletion of two amino acids: Arginine 176 (R176) and Glycine 177 (G177). **A1007, ¶BB.**

348. Bisgärd-Frantzen provides an alignment of alpha-amylases from *Bacillus amyloliquefaciens*, *Bacillus stearothermophilus* ("BSG"), and *Bacillus licheniformis;* and notes that they are highly homologous. **A1007, ¶CC; TE-177 at A8413:23-24; TE-101 at A7628:7-9.** Based on this homology, the PTO Examiner concluded that it would have been obvious to make Suzuki's BAN 176,177 deletions in the corresponding 179,180 positions of BSG, with an expectation of similar improvement. **TE-101 at A7628:13-19.**

349. Novozymes overcame this rejection with the Borchert Declaration, which describes an experiment comparing the deletion of R179-G180 in BSG to Suzuki's deletion of R176-G177 in BAN. **TE-508, A8857 at ¶ 3; TE-101, A776:6-11; A1008, ¶FF.** The experiment showed that the 179,180 BSG variant does not just provide a similar improvement: it is very much better. **TE-508, A8861-8862, ¶9; and A6550:16-22.** These results, confirmed at trial, demonstrate that the claimed invention is not obvious. *In re Soni*, 54 F.3d 746 (Fed. Cir. 1995) (non-obvious invention exhibits superior property or advantage that one of ordinary skill would have found unexpected). The improvement here was unforeseeable **A5641:10-19, A5618:8-**

6519:7; A6519:15-6520:13; A6522:7-12; A6529:7-19; and A6550:16-22. This has been borne out by Genencor's initial failures (**A5032:12-5039:11, A5046:14-21, A5048:13-5049:24**); Genencor's adoption of the invention claimed in the '031 patent (**TE200, A8532.1; A6538:22 - A6540:7; A6542:16 - A6543:5**), Genencor's commercial success (**A1006 ¶¶ V-Y**), and Genencor's own later patent application laying claim to the same subject matter. *Mosinee Paper Corp. v. James River Corp.*, 22 U.S.P.Q. 2d 1657, 1661 (E.D. Wis. 1992).

350. Dr. Borchert made a fair comparison of the claimed 179, 180 BSG variant with Suzuki's 176,177 BAN variant, and with the corresponding wild-type BSG and BAN alpha-amylases. **TE-508, A1008; A5640:19-5641:1; A6092:11-14.** He selected conditions that are relevant to the industrial applications where these enzymes are actually used, including low calcium, and an industrial temperature of 80 °C that was suitable for comparing all four enzymes. **A6092:15-25; A6534:2-14; A6536:2-11.** All of the enzymes were tested under the same conditions, as Dr. Borchert stated in his Declaration. **A6094:8-17; TE-508, A8858 ¶ 5.**

351. Dr. Borchert used equipement that made it reasonable to forego a pre-heated buffer (**A6538:19-20**), and which would not have changed the qualitative results and overall conclusion. **A6545:25.** Thermostability was compared by measuring the residual activity of each enzyme over time, with two readings per sample. **A6547:8-12.** Unreliable measurement were not counted, as any good scientist would do. **A6549:19-20**. The half-life of each enzymes was calculated using standard techniques, including a semi-logarithmic plot of the data and regression analysis. **TE-508, A8860; A6532:1-10.** The half-life is the time at which half (50%) of the initial alpha-amylase activity (100%) is still present under given conditions. **A5788:1-4.**

352. The experiment showed that Suzuki's BAN deletion increased thermostability 11-fold compared to the BAN wild-type enzyme. **A6532:11-14.** The corresponding BSG deletion caused a 63-fold increase in thermostability. ***Id.* at 15-23.; TE-508 at A8861.** The relative effect in BSG is 5.7-fold greater than BAN, reported as a 5-6 fold improvement in the

Borchert Declaration. **TE-508, A8660**; **A6533:18-6534:1.** Indeed, the BSG variant is still potent after exposure to high heat for 4,200 minutes (~ 3 days), and longer. **A6534:24-6535:4.**

353. According to Dr. Arnold., "[T]he practical effect is very apparent." **A6345:24.** "In fact, after three days it [the BSG variant] has more than half of its activity. So this is an enzyme that keeps working after days at 80 degrees centigrade" (**A6535:2-4**). This has a definite commercial impact, especially in fuel ethanol production, where alpha-amylases must work for hours at high temperatures and low calcium. **A6534:7-14; A6535:17-19.** Genencor itself admits that a lesser enzyme was unsuitable for demanding real-world conditions, and could not compete. **A5034:4-10;A5036:23-5037:14.**

354. This was a difference in kind and not just in degree. No one could have predicted so great a leap forward. **A5721:21-5722:4**. Before the invention in 1995, no one could have expected that a BSG enzyme with a half-life of ~1.5 hours at 80° C (**TE-508, A8860 ¶ 7**) could be increased to more than three days (***Id.***; **A6534:24-6535:4**). BAN wild-type and the BAN deletion variant, the closest prior art, had half-lives of less than 1 minute and less than 10 minutes, respectively, under the same conditions. ***Id***. Dr. Arnold found that an observed 63-fold improvement in BSG, or a 55 to 77-fold improvement ("the whole range of possibilities") (**A6549:4**), was unexpected and non-obvious, even with Genencor's critique. **A6550:16-19** (Arnold). Dr. Borchert himself was surprised. **A5641:10-19**. Dr. Klibanov said that anything less than an order of magnitude difference is unsurprising. But he did not support this assumption (**A5819:22-24**), and overlooked important industrial advantages. **A5018:20-5019:1; A5051:3-7; A6550:16-22.** Dr. Zeikus testified that there was, at best, a 50/50 chance that the 179,180 BSG deletion would even work. **A6107:2-13.** Genencor's Dr. Machius testified that in 1995, even with Suzuki, Bisgärd-Frantzen, and Machius '95, a person of ordinary skill (**A5721:21-25**):

> [W]ould not have been able to predict the magnitude of stabilization in BSG, or to compare, or to know if there was any stabilization at all.

See also **A5722:1-2; A5722:3-4.**

355. Genencor's own patent application (**TE-202**) discloses and claims the same BSG variants. **TE-202, at A8532.1 (Abstract); A8532.44 (claim 1); A6538:25-6540:6; A6542:20-6543:5**. While citing Suzuki and Machius '95 (**TE-202, A8532.14 at [0013]; A8532.20 at [0095]**), Genencor describes the 179,180 BSG variants as "providing desirable and unexpected results," and having "superior properties." **TE-202, A8532.22 at [0112], A8532.24 at [0123]**.

356. Genencor did not provide any experiments or data to challenge its conclusions. Second-guessing the experiment, with litigation hindsight, cannot be clear and convincing evidence that the claimed BSG variants are not as good as they really are; *i.e.*, that they are obvious and unpatentable. *Electro Med. Sys., S.A. v. Cooper Life Scis., Inc.* 34 F.3d 1048, 1055 (Fed. Cir. 1994) (no tests performed; "lack of hard evidence" and "opinion testimony unsupported by any backup" were unpersuasive against patentee's expert testimony and experiments.) As Dr. Arnold recognized (**A6650: 10-22**):

> [W]e've looked at ... every possible criticism. And my conclusion after seeing all of this is that it's a fair representation of what actually is going on with those enzymes. I would also like to mention that I have seen no counter data. This is not rocket science here. ... If this were wrong, if Borchert's data were far from the truth, I think I would have seen those data from some other place.

357. The claimed '031 patent variants provide an unexpected and commercially important advance, and are patentable over the closest prior art.

2. Machius Does Not Make the Claimed Variants Any Less Unexpected

358. A claimed invention may be obvious from one reference alone or from a combination of references. *Al-Site Corp.*, 174 F.3d at 1323. However, when obviousness is based upon a combination of references, the evidence must show some motivation to combine the prior art teachings that make the invention obvious: "A suggestion or motivation to combine generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art." *Al-Site Corp.*, 174 F.3d at 1323-24.

359. The mere identification of each element in the prior art, however, is insufficient to defeat the patentability of the combined subject matter as a whole. *In re Rouffet,* 149 F.3d at 1357. Rather, one must show that there were reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed and that there was a reasonable likelihood of success. *Id.; In re Dow Chem.,* 837 F.2d 469, 473 (Fed. Cir. 1988); *see also* 35 U.S.C. §103. Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure." *In re Dow Chem.,* 837 F.2d at 473.

360. "[T]he suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." *In re Rouffet,* 149 F.3d at 1358.

361. Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. *ACS Hosp. Sys.,* 732 F.2d at 1577; *Genzyme Corp.,* 315 F. Supp. 2d at 654.

362. Machius '95 does not add anything of value to the cited prior art. **A6530:3-8** The secondary structural elements proposed for BLA, from non-public X-ray coordinates (**A5718:1-15**), did not forecast the very highly improved thermostability of the claimed BSG variants. The Machius loop theory does not address, measure or even hint at the magnitude of improved thermostability that might be realized for other variants. **A5722:1-4.** Scientists propose endless theories (**A6526:5-6; A6527:19-23**), but Machius '95 even acknowledged that none were satisfactory. **TE-175, A8384.** The lack of further structural information about BAA and the Suzuki mutants was acknowledged as fatal (***Id.,* A8384-85**), to say nothing of the fact that there is no structural data about BSG at all.

363. According to Dr. Machius himself, Machius '95 says, at most, that the region corresponding to Suzuki's double-deletion in BAN is a "loop" on the surface of Domain B in BLA, which is enlarged in BAA by two extra residues. Theoretically, this could cause increased

mobility and decreased thermal stability of BAN v. BLA. **A5703:6-18.** *See also* **A5709:24-5710:11.** Nevertheless this does not provide any additional predictability; as Dr. Machius himself confirmed. **A5722:1-4; 21-25** (unable to predict fact or magnitude of stabilization in BSG).

364. Further, there were many problems with the BLA crystal structure referred to in Machius '95 (**TE-173, A8375**). It was not a reliable model from which to make predictions, and added nothing significant to what already could be taken from Suzuki, with or without Bisgärd-Frantzen. Whether Suzuki could be extrapolated to other mutants that really would work, and whether they would work as well as Novozymes discovered, was all unknown and unforeseeable: whether or not the artisan in 1995 was aware of the Machius loop. **A6529:11-15.**

365. Far from pointing the way to new and better variants, Machius '95 added more confusion to the literature. **A6530:3-8.** The loop idea is floated, and other theories trying to explain thermostability are discussed, but none are satisfactory, *e.g.*, because crucial data is missing. **TE-173, A8384; A6522:9-18.** Machius actually shows that engineering alpha-amylases to be more thermostable was (and is) an uncertain art. Genencor's Dr. Zeikus agreed (**A6103:17-22**) and added his own idea that "additional salt bridges is the feature that makes BLA more stable" (**A6524:21-6525:9**) -- not the loop, or any of the other ideas. **A6504:5-20; TE-178 at A8511.** No one in 1995, or today, knows why one alpha-amylase is more thermostable than another. No one could rely on Machius '95 to predict how successful the '031 variants would be. Dr. Machius himself admitted that "[l]oops, in general, can have any effect" and "knowing something that is a loop can either stabilize [a protein] or might destabilize it if you change that loop." **A5720:20-5721:3.** *See also* **A5721:19-5722:4.** There was no simple recipe for enhancing the properties of BSG. **A6509:10-6510:2.**

366. At most, Machius '95 only makes it obvious to try the same deletion in another alpha-amylase like BSG. Neither Machius '95 alone or in combination with Suzuki or Bisgaard-Frantzen give rise to a reasonable likelihood of success, however. Genencor's expert, Dr. Zeikus summarized best what one of ordinary skill in the art would take away from Machius '95: "Hey,

it worked on one enzyme, why not try it on another enzyme." **A6107:6-7.** "Obvious to try" is not the standard under 35 U.S.C. 103. *In re Duel,* 51 F.3d 1552, 1559 (Fed. Cir. 1995).

3. Other Secondary Considerations Belie a Finding of Obviousness

367. Secondary considerations of non-obviousness also help to avoid hindsight and to promote a fair adjudication on questions of obviousness. *Graham*, 383 U.S. at 17-18; *In re Rouffet*, 149 F.3d at 1357-58 (secondary considerations are essential components of the obviousness determination). These considerations include (i) long felt need, (ii) failure of others, and (iii) commercial success. *Graham*, 383 U.S. at 17-18; *In re Rouffet*, 149 F.3d at 1355.

368. Here, there was a long felt need. Dr. Crabbe testified that Genencor's customers were in need of a more economical and thermostable alpha-amylase for several years. Genencor could not meet this need until it offered Spezyme Ethyl. **A5032:19-5033:9.** It has enabled Genencor to compete in the fuel ethanol liquefaction market. **A5049:18-24.** Genencor's G997 and Spezyme Fred patents were not good enough (**A5034:4-5035:2; A5037:3-14**), nor was Genencor able to improve Spezyme Fred. **A5046:14-21; A5048-5049:25.**

369. When the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988) (commercial success of infringing product demonstrated non-obviousness). Genencor admits that it needed Spezyme Ethyl to compete successfully. **A5032:19-5033:9**

370. Spezyme Ethyl has been also a commercial success. In just two years, total annual sales of Spezyme Ethyl have almost tripled. **A1006, ¶ Y.** Spezyme Ethyl has enjoyed great success, at the direct expense of Novozymes. **A6028:14-22.**

371. This commercial success, and that others tried and failed to reach a solution, favors a finding of non-obviousness. *Demaco,* 851 F.2d at 1391.

372. Finally, Genencor filed its own patent application in 2004, claiming the Spezyme Ethyl alpha-amylase. **A6538:22-6540:7; A6542:16-6543:5.** All of the prior art asserted against

the '031 patent is prior art to Genencor. Yet, Genencor represented to the PTO that Spezyme Ethyl is still non-obvious and patentable. As late as April 2005 (**TE-202, A8532.1**), Genencor said there was a long-felt need for alpha-amylases having improved thermostability (***Id.* at [0015]**), and that 179,180 *B. stearothermophilus* variants provide unexpected, superior performance (***Id.* at [0112]**), especially for starch liquefaction (**TE-202, [0111]**). This is telling evidence of non-obviousness. *Mosinee Paper Corp.*, 22 U.S.P.Q. 2d at 1661; *American Med. Sys., Inc. v. Medical Eng'g Corp.*, 794 F. Supp. 1370, 1386 (E.D. Wis. 1992) (attempt to patent same subject matter shows infringer believed it was new and non-obvious); *Polaroid Corp. v. Eastman Kodak Co.*, 228 U.S.P.Q. 313, 321 (D. Mass. 1985) (attempt to patent accused product is evidence that claims are valid against the prior art); *Colt Indus. Operating Corp. v. Index-Werke KG*, 205 U.S.P.Q. 990, 1002 (D.D.C. 1979) (such actions "are of significant value in showing the thinking of those skilled in the art, and as such, tend to show that the patented invention was not obvious").

373. In sum, the Suzuki and Bisgard-Frantzen references do not make the '031 Patent obvious because they only provide an invitation to experiment with regard to the Suzuki double deletion in BSG, and an invitation to experiment is not enough. Novozymes overcame the examiner's obviousness rejection over these by showing the dramatic and unexpected increase of thermal stability in the claimed variant. Novozymes conducted a scientifically appropriate thermal inactivation experiment that resulted in the reliable and unexpected thermal activation results, which Novozymes accurately presented to the examiner.

374. The Machius reference does not factor into the obviousness determination because (i) it provides no further motivation to attempt the Suzuki double deletions in BSG; (ii) it does not provide a basis to predict the dramatic and unexpected increase in thermal stability accomplished by the '031 variant; and (iii) it simply created more confusion in the already confusing art of protein engineering with alpha-amylases.

375. A review of the relevant secondary considerations—such as a long felt but unresolved need, failure by others, and commercial success—provides objective evidence of the non-obviousness of the '031 invention. Finally, Genencor's ongoing attempt to patent the same invention is strong evidence that Defendants believe the '031 invention to be non-obvious. Defendants have not carried their heavy burden of proving obviousness by clear and convincing evidence.

4. The '031 Patent contains an enabling written description

376. Section 112 of the patent statute requires the specification to be "enabling" to a person "skilled in the art to which [the invention] pertains, or with which it is most nearly connected." 35 U.S.C. §112 (first paragraph). "[T]o be enabling, a specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'". *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) (citation omitted); *see In re Wands*, 858 F.2d 731, 735-37 (Fed. Cir. 1988).

377. "[I]t is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation." *Johns Hopkins Univ.*, 152 F.3d at 1360.

378. As long as the experimentation needed to practice the invention is not "undue," enablement is not precluded by the necessity for some experimentation. *In re Wands*, 858 F.2d at 736-37. Whether the experimentation needed to practice the invention is undue depends on several factors identified by the *In re Wands* court:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. at 737.

379. Additionally, in determining whether a specification is enabling, the Federal Circuit has emphasized that a "patent need not disclose what is well known in the art." *Id.* at 735.

Paragraph 1 of section 112 permits enablement of the claimed invention with "materials outside of the specification" in order to avoid encumbering the specification with all the knowledge already known concerning how to make and use the claimed invention. *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 1382 (Fed. Cir. 1999).

380. The party challenging enablement of the invention under section 112 must carry the heavy burden of proving a lack of enablement by clear and convincing evidence. 35 U.S.C. § 282; *Johns Hopkins Univ.*, 152 F.3d at 1359; *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1469 (Fed. Cir. 1993).

381. The '031 patent is fully enabling. The PTO Examiner specifically considered this question. She rejected Novozymes' original claims specifying "at least 80% homology," but concluded that the specification is enabling "for an alpha-amylase having at least 90% homology to SEQ. ID NO. 3." **A7721:10-11.** The claims were further narrowed to recite "at least 95% homology," and to specify that the claimed variants have "alpha-amylase activity" **(TE-101, A7734),** prompting the PTO Examiner to withdraw the enablement rejection.

382. The claimed variants can be made without undue experimentation, using the tools readily available to protein engineers. The '031 patent provides extensive guidance on the construction of variants (**TE-100, A7012-7013**), as well as assays for detecting variants that have alpha-amylase activity. ***Id.*, A7022 at 30:55-31:27.** Dr. Borchert used the same type of assay to measure alpha-amylase activity in his Declaration. **TE-508, A8858 at ¶ 5** (Experimental Protocol); **A6078:24-25.** Dr. Klibanov also described the same type of routine assay (**A5786:14-5787:4**), and testified that he could prepare an alpha-amylase with the two deletions 179,180 in a *B. stearothermophilus* alpha-amylase by simply following the teachings in the Suzuki paper. **A6005:18-6006:5.**

D. The '031 Patent Is Enforceable

1. There Was No Inequitable Conduct

383. Genencor has alleged that the '031 patent is unenforceable due to acts of inequitable conduct on the part of various Novozymes personnel. These allegations exemplify the Federal Circuit's oft-cited, disapproving observation made more than 17 years ago -- and which is just as valid today -- that the "habit of charging inequitable conduct in almost every major patent case has become an absolute plague." *Burlington Indus., Inc. v. Dayco Corp.*, 849 F.2d 1418, 1422 (Fed. Cir. 1988), (cited in *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 876 n.15 (Fed. Cir. 1988) and *ISCO Int'l, Inc. v. Conductus, Inc.*, 279 F. Supp. 2d 489, 505-06 (D. Del. 2003)).

384. Patent applicants and their attorneys have a duty of candor in the PTO. 37 CFR § 1.56(b) (1992). To establish a breach of that duty, or "inequitable conduct," it must be conspicuously shown "that material information was intentionally withheld for the purpose of misleading or deceiving the patent examiner." *Allied Colloids, Inc. v. American Cyanamid Co.*, 64 F.3d 1570, 1578 (Fed. Cir. 1995).

385. Materiality and intent are distinct factual inquiries, and must each be shown by clear and convincing evidence. *Purdue Pharma, L.P. v. Endo Pharms., Inc.*, 438 F.3d 1123, 1128-29 (Fed. Cir. 2006); *Digital Control, Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1313 (Fed. Cir. 2006).

386. Whether information is material is determined by PTO regulations. *Purdue Pharma*, 438 F.3d at 1129. Information is material to patentability when (37 CFR § 1.56(b) (1992)):

> it is not cumulative to information already of record or being made of record in the application, and (1) it establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or (2) it refutes, or is inconsistent with, a position the applicant takes in (i) opposing an argument of unpatentability relied on by the [PTO] or (ii) asserting an argument of patentability.

This was the standard after 1992 and during the '031 prosecution. *See Purdue Pharma,* 438 F.3d at 1129.

387. Under an older standard, information was material when there was a substantial likelihood that a reasonable examiner would consider it important in deciding patentability. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1363 (Fed. Cir. 2003). The Federal Circuit still relies on the older rule, tempered by what the new rule indicates is important. *Digital Control*, 437 F.3d at 1316.

388. Information is categorically not material if it is cumulative of what was already before the PTO; *i.e.*, "if the reference teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO." *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1574-75 (Fed. Cir. 1997); *see also Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1582 (Fed. Cir. 1991). Less relevant information is not material either. *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1567-77 (Fed. Cir. 1996); *Haliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1440 (Fed. Cir. 1991).

389. Inequitable conduct also requires definite proof of culpable intent. "Materiality does not presume intent, which is a separate and essential component of inequitable conduct." *Atofina v. Great Lakes Corp.*, 441 F.3d 991, 1002-03 (Fed. Cir. 2006) (intent wrongly inferred from failure to provide full translation of reference).

390. Intent should not be too easily inferred from circumstance, particularly when there is a reasonable explanation for what happened. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 939 (Fed. Cir. 2003) (noting the ease with which a relatively routine act can be portrayed as misleading). Accordingly, "[i]ntent to deceive can not [*sic*] be inferred solely from the fact that information was not disclosed." *Hebert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). A court may not infer deceit, akin to a fraud, "simply from the decision to withhold a reference where the reasons given for the withholding are plausible." *Dayco Prods., Inc.*, 329 F.3d at 1367.

391. Likewise, gross negligence is not inequitable; the "involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown Med. Consultants,* 863 F.2d at 876.

392. If the court finds threshold levels of materiality and intent, it still must carefully balance them, for example: "the less material the information, the greater the proof [of intent] must be." *Purdue Pharma*, 438 F.3d at 1135; *see also CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1343 (Fed. Cir. 2003). This is an equitable determination: was the applicant's conduct so egregious and culpable that the patent should not be enforced. *Kingsdown*, 863 F.2d at 875; 877.

(a) Machius '95

393. Here, Novozymes did not cite the Machius '95 reference; but this was not inequitable. At most, Machius was cumulative of Suzuki and Bisgärd-Frantzen, already before the Examiner. **A6102:14:25; A6530:3-18.** Moreover, there is evidence of good faith and no evidence of intent to deceive the PTO. *Kingsdown*, 863 F.2d at 876.

394. Neither Mr. Garbell nor Dr. Borchert, after carefully considering Machius '95 in an *inter partes* PTO interference involving a different patent, saw Machius '95 as material, there or here. **TE-524, A8915-17; A5599:11-24; A5632:8-5638:23, A5662:8-12, A5672:11-5674:14, A6115:16-6118:11, A6503:24-6505:14, A6506:18-6507:4, A6509:2-6510:6, A6514:10-25, A6515:16-6526:14, A6527:13-6530:18.** Machius '95 does not establish unpatentability or contradict any position taken by Novozymes. 37 C.F.R. § 1.56(b).

395. The uncertain Machius crystal structure was particularly off-base. The '031 patent claims concern amino acid changes (like Suzuki), not a crystal structure *per se*, as in the interference where Novozymes did cite Machius '95. **A5657:15-19.** There were also serious problems with Machius that were identified by Dr. Borchert. **TE-524, A8915-19.** Machius is less

relevant than Suzuki, at most is cumulative, and did not have to be given to the PTO. **A5641:2-6, A5660:12-18**

396. Mr. Garbell did not think Machius added anything to what the Examiner already had before her. **A5672:14-17; A5673:5-10; A5673:19-21; A5675:9-20.** Based on his own review from the interference and his close working relationship with Dr. Borchert, Mr. Garbell did not find a reason to consult further with Dr. Borchert, nor did Dr. Borchert feel differently. **A5673:11-5674:14.**

397. Notably, Mr. Garbell was aware of and consistently strove to meet his duty of disclosure to the PTO. He did not experience any doubt about the immateriality of Machius '95 or whether it should be cited. **A5676:25-5677:4; A5662:8-12.**

398. Dr. Borchert read Machius '95 shortly after it was published and during the interference. **A5591:22-5592:5.** He had many conversations about Machius '95 with Mr. Garbell. **A5671:16-5672:2; A5676:4-8,** and with help from Mr. Garbell, Dr. Borchert even prepared a declaration submitted in the interference (**TE-524**), which discusses Machius '95. **A5601:10-25; A5602:6-5603:3.** Still, and for good reason, neither of them saw Machius '95 as material to the '031 prosecution. **A5645:21-5646:4; A5673:11-19; A5674:1-14.**

399. The interference provides contemporaneous evidence of good faith rather than intent to mislead. *See* **TE-524; A8931; TE-508; A-8862.** Dr. Borchert and Mr. Garbell believed that Machius was fatally flawed: *e.g.,* it did not provide the coordinates necessary for a reliable structure, and it referred to a calcium-depleted, cleaved protein, which was of very limited use. **TE-524; A-8915-17.** Given these views, the crystal structure claims in the interference as opposed to the '031 patent variant protein claims, and the reliance by the '031 patent PTO examiner on Suzuki and Bisgärd-Frantzen, there is a reasonable explanation for not citing Machius '95. There is no clear and convincing deceptive intent, and no inequitable conduct.

400. Objectively, Machius '95 is cumulative prior art at best. It could not have been "inequitable" to forego citing it. *FMC Corp., v. Manitowoc Co.,* 835 F.2d 1141, 1415 (Fed. Cir.

1987). Machius discusses Suzuki, but does nothing more to help a protein engineer make and use the variants Suzuki already disclosed, nor variants which might be extrapolated from Suzuki. **A6517:13-6523:4.** Machius '95 is based on a distorted X-ray model and disputes the very theories it presents on thermostability. ***Id.*; A5635:15-20, A5716:11-5718:22, A5724:25-5725:8, A5725:23-5727:12, A5729:23-5731:21.** Machius '95 adds uncertainty; it does not clarify any questions or solve any problems. In fact, Machius '95 is evidence that designing better proteins remained unpredictable, could not use speculative theories, relied on trial and error, and did not affect Suzuki's empirical results. **A5632:8-5638:23, A5662:8-12, A5672:11-5674:14, A6115:16-6118:11, A6503:24-6505:14, A6506:18-6507:4, A6509:2-6510:6, A6514:10-25, A6515:16-6526:14, A6527:13-6530:18.**

401. Since Machius was at best cumulative, not citing Machius to the PTO cannot constitute inequitable conduct. The record cannot support a finding of culpable intent either, and a weighing of all the evidence precludes a judgment of unenforceability. **A5662:8-12, A5673:5-11, A5676:19-5677:4**

(b) <u>The Borchert Declaration</u>

402. The Borchert Declaration was not inequitable either. It appropriately reported a fair experiment showing the relative improvement of the claimed alpha-amylase variants compared to the Suzuki variants, and to their wild-type parent enzymes. **A6549:23-6550:15**

403. Novozymes gave experimental data to the PTO in the Borchert Declaration. **TE-508.** The 179,180 BSG deletion was fairly and properly compared with the closest prior art: Suzuki's 176,177 BAN deletion. ***Id.*, A8857-8 at ¶3,4; A5660:17-19; A5585:10-11; A5596:2-9.** Thermal inactivation tests showed that the improved thermostability for BSG was unpredictably high compared to the BAN. *Id.*, **A8861-2, ¶9.**

404. Dr. Borchert set out to do a fair and reliable comparison of the effect this deletion has on thermostability. **A5460:19-5410:1; A6092:11-14.** He designed the experiment and drafted his Declaration with help from Mr. Garbell. They discussed that good (desired) and bad

(undesired) results must be presented to the PTO. **A5662:13-18; A5665:10-19; A5666:2-11; A5677:5-21.** The work was done in Denmark by Dr. Borchert and Novozymes' technicians. **A5586:10-14, A5641:20-5642:3, A6073:10-6074:5** Mr. Garbell had no reason to question the resulting data he was given. He was not aware that any readings were discounted. **A5664:25-5665:9.** In fact, a few raw data points were not used by Dr. Borchert or his technician, but for a proper scientific reason - they were scientifically unreliable. **A5614:25-5617:19, A5643:2-5645:17, A6546:1-6548:5, A6549:7-20.**

405. Dr. Borchert's work was well-designed, properly conducted under industrially relevant and fair conditions, and honestly reported. The experiment used an industrially relevant, low calcium concentration (0.1 mM) (**TE-508, A8858-8859, ¶ 5**), as in the patent (**TE-100 at 30:62-67**). Reduced calcium was a particular goal of the invention. ***Id.*** **at 1:21-24, 2:61-66, 4:7-12; A6092:15-25; A6114:18-20; A6535:20-6536:11.** The experiment was done at 80 °C (**TE-508, A8858-59, ¶5**), which was "a fair temperature to choose" (**A6536:24-25**), especially for an industrial enzyme (**A6536:12-6537:25**). Tests showed that the BAN and BSG could be evenly compared at this temperature. **A6067:21-6077:4; A6094:8- A6096:6.** The test buffer was not preheated, but this was reasonable with the thin test-tubes and pre-heated equipment that was used. **A5628:4-7; A6078:12-15; A5613:21-5614:13; A6075:5-14; A6538:17-21; A6541:12-19.** Additional work showed that "ramp-up time" was not a real problem; a preheated buffer would not have materially changed the outcome. **A6544:3-11; A6545:22-25; A6045:3-25; A6046:17-6047:2; A6047:3-6050:11; TE-218.** Genencor does not use a pre-heated buffer either, for the same tests on the same enzymes. **TE-202, A8532.25** (Example 3); **A6538:24-6539:4; A6539:13-6541:3.** The data analysis was reliable, including log plots and regression analysis to determine half-life. These are standard methods, and are used the same way by Genencor. **A5762:8-18; A6542:7-6543:5; TE-202.**

406. Each sample was read twice. **A6076:6-8; A5767:15-5768:15.** Two BSG wild-type readings at 20 and 40 minutes were contaminated by substrate in the samples and could not

be used, but the two parallel readings were acceptable and were used. **A6080:3-14**; **A5770:15-5771:6**. One BSG variant sample at 2881 minutes had evaporated, and both of its readings could not be used. **A6079:5-14**; **A5643:17-24**; **A6079:5-9**; **A6549:7-20**; **A6020:14-24**. Another BSG variant sample at 2940 minutes gave two widely different readings, with a 102-130% difference between them, one of which showed more enzyme activity after two days of heating than at the start of the experiment (>100%). This was highly questionable, and those two readings could not be used with any confidence. **A5643:25-5644:2**; **A5768:23-5769:3**; **A5645:8-17**; **A6022:11-13**.

407. These were honest and reasonable judgments of the kind made by scientists every day. **A6549:10-20.** The experiment showed what was really going on, and the questioned readings would not change the overall result. **A6550:16-22**. The thermostability of the BSG variant is unpredictably high vs. its wild-type, compared to Suzuki's BAN variant vs. its wild-type. ***Id***.

408. Dr. Borchert's experiments and the results in the Declaration are trustworthy, and show substantial and surprising improvements in thermostability for the claimed alpha-amylase variants. Novozymes did not withhold or misrepresent material information. There was no intent to mislead the PTO. There was no inequitable conduct. There is no evidence of culpability so clear and convincing that the '031 patent should be struck down. *Kingsdown*, 863 F.2d at 876.

2. <u>There Was No Prosecution Laches</u>

409. To prove prosecution laches, Genencor must present clear and convincing evidence that Novozymes unreasonably and inexplicably delayed prosecution of the '031 Patent. *Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP*, 422 F.3d 1378, 1385, amended, 429 F.3d 1051 (Fed. Cir. 2005); *Stambler v. RSA Sec., Inc.*, 243 F. Supp. 2d 74, 76 (D. Del. 2003). Prosecution laches "should be applied only in egregious cases of misuse of the statutory patent system." *Symbol*, 422 F.3d at 1385. Egregious misuse means "a pattern of unjustifiably delayed prosecution" designed to extend the term of a patent, *e.g.*, the deliberate 18

to 39 year delay in *Symbol*, *id.* at 1385-86, or the 12 consecutive "file wrapper continuations" employed in *In re Bogese II*, 303 F.3d 1362, 1365, 1369 (Fed. Cir. 2002).

410. Genencor could not and did not show inexplicable delay or egregious misuse of process. On the contrary, Novozymes diligently prosecuted both the '031 Patent and the family of applications from which it arose. **TE-101, A7042, A7136** (summarizing the '031 family history, including two prior applications that issued as patents) Novozymes neither engaged in dilatory tactics, nor ambushed an industry with "submarine patenting."

411. The '031 claims deliberately encompass Spezyme Ethyl. Patentees are permitted to tailor their claims to cover a competitor's product, even when the product is discovered during prosecution. *Kingsdown*, 863 F.2d at 874. There is "nothing improper, illegal or inequitable in filing a patent application for the purpose of obtaining a right to exclude a known competitor's product from the market." *Id.* "Nor is it in any manner improper to amend or insert claims intended to cover a competitor's product . . . learned about during the prosecution of a patent application." *Id.*

412. Here, Novozymes was already pursuing the claims for the subject matter at issue in this case (**TE-101, A7045-7048**), long before Genencor introduced Spezyme Ethyl in April 2004. **A-1006**; **A5663:13-22**. The PTO initially rejected these claims as obvious, requiring some time by Novozymes to address the rejection. *Symbol*, 422 F.3d at 1385 (delays and refilings associated with the need to overcome a rejection legitimate and justifiable); **A1007-1008; TE-101, A7619-7631, A7717-7760; A7791-7802.** Genencor even had notice of claims potentially encompassing Spezyme Ethyl, because the application was published on April 3, 2003. **A5663:16-5664:21**. *See also,* **A5014:4-14** (actual notice). Accordingly, Genencor has not and cannot meet their burden of proving prosecution laches by clear and convincing evidence.

Respectfully submitted,

Dated: April 21, 2006

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CERTIFICATE OF SERVICE

I, Andrew A. Lundgren, hereby certify that on April 21, 2006, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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